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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,221	12/13/2001	Nathan S. Lewis	CIT1300-1	9894

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EXAMINER	
NOGUEROLA, ALEXANDER STEPHAN	
ART UNIT	PAPER NUMBER
1753	

DATE MAILED: 10/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,221	LEWIS ET AL.	
	Examiner	Art Unit	
	ALEX NOGUEROLA	1753	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *amendment of August 08, 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/15/2005*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. The amendment of August 08, 2005 does not render the application allowable.

Response to Arguments

2. Applicant's arguments filed August 08, 2005 ("Amendment") have been fully considered but they are not persuasive. On the bottom of page 6 of the Amendment, bridging to page 7 Applicants describe how their sensor array may be enabled to identify a structure, function and/or activity associated with a monacylglycerol or lipid.

> The sensors of the sensor array interact with the analyte based upon the chemical structure of the analyte e.g., its side-groups, charge and the like). for example, a sensor array comprising 5 sensors may include a first sensor capable of detecting an alcohol, a second sensor capable of detecting a hydrocarbon, a third sensor capable of detecting a halide, a fourth sensor capable of detecting an aromatic and a fifth sensor capable of detecting an ester. When a sensor array is contacted with an analyte (e.g., a monoacylglycerol comprising an alcohol group and a long chain hydrocarbon) the sensor array would provide a signal profile demonstrating a change in sensors 1 and 2 and not in 3-5. This signal profile would then be compared to a library and a closest match would be provided indicating that eh tested analyte has a structure similar to a lipid and identifying a structure, function and/or activity associate with, for example, a monoacylglycerol, lipid etc. If the analyte comprises a hydrocarbon, alcohol and ester, the sensor profile would indicate sensors 1, 2 and 5 react or change in response to the analyte while sensors 3 and 4 do not. Even the absence of change is important in a signal profile.

> Such an analyte would be characterized as having a function, property and/or activity associated with a fatty acid.

First, the examiner has not found support for such a sensor array in the original disclosure. In the sensor array described above the sensors of the sensor array are each specific to a certain functional group. Applicants are requested to indentify where in the original disclosure such a sensor array is mentioned or suggested. Second, the sensor array described above is actually contrary to the sensor array of the original disclosure:

> "The present invention utilizes a different approach [from the prior art]. A plurality of differentially responsive sensors, each of which provides measurable signals in response to a variety of analytes, chemicals, and biochemicals of concern is used. The desired chemical or biological activity is not revealed by the response of an individual sensor or individual sensor response signal, but is instead obtained by pattern analysis of the responses produced by a plurality of differentially responsive sensors in the sensor array device. [emphasis added] " See paragraph [0018] of the specification.
>
> 'By "differentially responsive sensors" is meant any number of sensors that respond to the presence of a collection of molecules with the sensor by providing some measurable change. [emphasis added]' See paragraph [0016] of the specification.

Third, Applicants have not explained how magnetic and mechanical sensors (claim 11) could be used to distinguish a hydrocarbon functional group from an alcohol group. Last, as Applicants are aware, a function, property and/or activity of a chemical or biochemical species is not just determined by its composition, but also by its sequence and higher order structure, especially for high molecular weight, complex molecules such as proteins, antigens, enzymes, and nucleic acids. A genetic mutation

or denaturing may result in a gene or protein with the same composition as before the change, but a dramatic change in function, property and/or activity. Thus, just sensing the presence of certain functional groups will possibly reveal the function and/or activity of only simple, small molecules.

Applicants direct the Examiner's attention to U.S. Patent No. 5,424,959. See page 8 of the Amendment. This patent actually works against Applicants. Unlike Applicants claimed invention the claims of U.S. Patent No. 5,424,959 are modest. Claim 1 requires a plurality of artificial intelligence modules capable of estimating the *content* of fluid being monitored. Independent claim 5 makes "an accurate determination of the *content* of the unknown fluid mixture. [emphasis added]," not a property, function and/or activity of the fluid or a fluid constituent. The claims of U.S. Patent No. 5,424,959 are restricted to hydrocarbons, not every possible chemical or biochemical from alcohols to proteins and nucleic acids. Finally, the claims of U.S. Patent No. 5,424,959 refer to only one sensor type – a fluorescence detector, which is a known technique for indentifying hydrocarbons (col. 1:13-26 in U.S. Patent No. 5,424,959).

Applicants assert,

> "Applicants' invention, by analogy, utilizes the interactions of structural side-groups, charges etc. to predict a function. However, according to the paragraph quoted above, these algorithms, which are currently patented and on the market, lack enablement because such functions are 'rarely predictable'. Should the Examiner wish, Applicants can provide numerous examples of protein-function-prediction based solely on the full or partial structure of an unknown protein.' See the bottom of page 9 of the Amendment bridging to page 10

The Examiner invites Applicants to submit examples of protein-function-prediction based solely on detecting side groups present in a protein, especially using mechanical and magnetic sensors.

Applicants refer to Severin et al., Anal. Chem. 72:2008-2015, 2000, for enablement for a broad of sensor types. See the bottom of page 10 of the Amendment, bridging to page 11. However, decting small gas phase molecules, such as hexane and 2-propanol, with an array of mechanical sensors does not enable predicting the function and/or activity of proteins, antigens, enzymes, and nucleic acids.

Applicants mistakenly makes an assumption about transduction modalities and sensor compositions that is inaccurate. Applicants state, "It is the material(s) of the sensors that determine their ability to interact with an analyte. The transduction/measuring of that interaction can be done any number of ways... in other words, the polymers themselves would be interacting with the analyte in a similar fashion, but the transducers would be merely be optical or mechanical compared to electrical." See page 11 of the amendment. Applicants assume that the interaction between an analyte and the sensing region of a sensor, such as a polymer, can be detected by any transducer no matter what the nature of the resulting property change in the polymer due to its interaction with the polymer. The transduction modality must be of a nature related to the nature of the change produced by the interaction between the analyte and the polymer. If the analyte-polymer interaction produces only an optical change in the polymer then an optical transducer modality must be used to detect this change, not a mechanical, electrical or magnetic modality. Now the analyte-polymer

interaction may produce more than one type of change, which can be correlated, but this is not the same as one type of change in the polymer being detected by different transducer modalities. In the Severin et al., Anal. Chem. 72:2008-2015, 2000, the authors of the article found "[t]he data indicate that the dc resistance change is directly relatable to the thickness change of the polymers ..." (abstract), however, it is noteworthy that resistances 'were measured using a 2002 digital multimeter" (third full paragraph in the first column on page 2010), that is, the electrical property change was measured using an electrical meter. As asked on page 6 of the Office action of May 10, 2005,

> "Are Applicants asserting that merely by using the same polymer used in an array of electrical resistances for predicting the inhibitory activity of gaseous alcohols on cytochrome P-450 aniline hydroxylation instead in an optical, mechanical, or magnetic sensor array of choice the optical, mechanical, or magnetic sensor array so modified will then be able to predict the inhibitory activity of gaseous alcohols on cytochrome P-450 aniline hydroxylation?"

Applicants state, "the Examiner will recognize that any number of sensor types and sensor modalities can be used in the claimed invention." See page 12 of the Amendment. The Examiner does so recognize. The issue though is whether undue experimentation would be required for the wide scope of analytes and sensor types.

Status of the Rejections pending Since the Office action of May 10, 2005 and the Supplemental Office action of June 08, 2005

3. The rejections of claims 1-15 under 35 U.S.C. 112, first paragraph, are withdrawn.

4. The rejection of claim 16 under 35 U.S.C. 112, first paragraph, is maintained.

5. The rejections of claim 16 under 35 U.S.C. 112, second paragraph, are withdrawn.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 9-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for predicting the inhibitory action of alcohols on cytochrome P-450 aniline p-hydroxylation and perhaps some other properties of alcohols or simple organic molecules, such as vapor pressure, does not reasonably

provide enablement for predicting or determining the specific activity, chemical or physical property, or function of compounds other than alcohols. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicants claim a device that can predict or determine the specific activity, chemical or physical property, or function of an unknown analyte by comparing its signal profile from a sensor array to a collection of sensor array signal profiles from other substances. Claim 16 is unbounded in terms of what the analyte can be and what specific activity, chemical or physical property, or function can be determined or predicted. The last paragraph of claim 16 uses the open term "comprises" and lists a very extensive list of organic functional groups. In the Office action of June 08, 2005 the Examiner asked whether the limitation in the last paragraph of claim 16 means that the primary functionality of the analyte is one of the listed functionalities, or whether, for example, a DNA molecule would be an analyte as contemplated by claim 16. Since Applicants have not commented one way or the other, the examiner assumes that analytes such as those listed in original claims 4-7 are considered to be within the scope of claim 16.

Claim 16 is also unbounded as to the type of sensor array. Claim 11 states that the sensors may change optically, electrically, magnetically, mechanically, physically, or a combination thereof.

The invention of claims 9-16 is of a complex nature as it uses a computer-supported system not to identify or quantitate, but to determine specific activities,

chemical or physical properties, or functions of an unlimited scope of analytes including enzymes and nucleic acids with any type of sensor array.

A review of related work in the field shows that others have limited themselves to more modest goals of predicting a particular property on a select type of analyte, such as monitoring sausage fermentation[1], predicting gasoline properties[2], or discriminating chirality with simple gas sensors[3].

The specific activities, chemical or physical properties, or functions of analytes such as antibodies, enzymes, proteins and nucleic acids are rarely predictable. If otherwise, there would be no need for the many hundreds of journal articles on these substances written in dozens of biochemical and chemical journals each year. Old Yellow Enzyme, an arbitrary choice, is illustrative. Although it had been discovered and purified almost 60 years before the time of the invention of the claimed invention and much research had been done on this substance it was only in the few years prior to the invention of the claimed invention that the enzymatic properties and structure-function relations were better understood. Its physiologic role is still unknown. See the Coordinating Editor's comment and the abstract in "Flavoprotein Structure and Mechanism 8 – Structure-function relations for old yellow enzyme" by Karplus et al. The FASEB Journal, vol. 9, December 1995.

Applicant's only example in his disclosure is predicting "the inhibitory action of a series of alcohols on cytrochrome P-450 aniline p-hydroxylation" (described on pages

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[1] Ekov et al. « Monitoring sausage fermentation using an electronic nose, » Journal of the Science of Food and Agriculture (1998), 76(4), 525-532.
[2] Litani-Barzlai et al. « Online remote prediction of gasoline properties by combined optical methods, » Analytica Chimica Acta (1997), 339(1-2), 193-199.

22-35 of the specification). This involves passing gas phase alcohols over the sensor array to "train" it with alcohols used as standards and to test the sensor array with unknown alcohols. With only this example as guidance one with ordinary skill in the art would not be able to use Applicant's invention to predict the specific activity, a binding activity, an inhibitory activity, or a modulating activity of an enzyme, let alone predict the secondary, tertiary, or quaternary structures of proteins, or predict the functions of various antibodies or antigens or RNA or DNA sequences, without undue experimentation, if such predictions could be made at all using a sensor array response profile. Should enzymes, proteins, and nucleic acids be also put into the gas phase and passed over the same array of sensors? How is one with ordinary skill in the art to select the right sensor for the unknown analyte of interest and the specific activity, chemical or physical property, or function of the analtye to be predicted? Can crystalline colloidal array sensors and capacitance sensors (claim 12) be used for enzymes and antibodies? Can these sensors be used to determine any specific activity, chemical or physical property, or function of enzymes and antibodies? How is a magnetic sensor array to be used to predict the inhibitory action of alcohols on cytochrome P-450 aniline p-hydroxylation?

Thus, the scope of claims 9-16 is too broad because of the almost unlimited scope of the claims in terms of analyte and analyte property, the state of the art and relative skill in the art at the time of invention, the limited guidance and example provided by Applicant's disclosure, the unpredictability of properties of various proteins,

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[3] Bodenh ¯er et al., « Chiral discrimination by Simple Gas sensors, » Transducers '97, June 16-19, 1997

enzymes, antibodies, DNA and RNA, and the undue experimentation required to use the analyte screening system.

8. Claims 9-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants are requested to clarify whether all or any of the analytes of original claims 4-7 should be considered to be within the scope of claims 9-16, more particularly, whether an analyte of original claims 4-7 would be an analyte as set forth in the last paragraph of claim 16.

Information Disclosure Statement

9. Applicants are requested to provide a copy of the Toppare article cited on sheet 4 of the Information Disclosure Statement of September 15, 2005, which the examiner has not found in the electronic file for the application.

Final Rejection

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEX NOGUEROLA whose telephone number is (571) 272-1343. The examiner can normally be reached on M-F 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, NAM NGUYEN can be reached on (571) 272-1342. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Alex Noguerola
Primary Examiner
AU 1753
October 21, 2005